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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,692	01/16/2002	Darrell H. Carney	3033.1002-004	6715

21005 7590 08/20/2003

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	13

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,692	CARNEY ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *6-10 and 20-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11-19 and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-46* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8, 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Status of Application, Amendments and/or Claims

The information disclosure statement filed 23 July 2002 (Paper No. 8) and 15 November 2002 (Paper No. 9) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The amendment filed 27 May 2003 (Paper No. 12) has been entered in full. Applicant's election with traverse of Group I (claims 1-19 and 41-46) and SEQ ID NO:6 in Paper No. 12 is acknowledged. The Examiner will rejoin SEQ ID NO:5 and SEQ ID NO:6.

The traversal is based on the second restriction requirement. The traversal is on the grounds that it would be unduly burdensome to require an Applicant to individually prosecute every species within a genus. Applicant cites MPEP 809.03. Applicant asserts that the claims of the instant application are inseparable from numerous linking claims, e.g. independent Claim 1, drawn in part to an agonist of the non-proteolytically activated thrombin receptor. Applicant maintains that each claim in the instant application is drawn, at least in part to a species contained within the genus defined by claim 1. Claim 1 links the claims and acts to prevent restriction between them.

Applicant's arguments have been fully considered and deemed persuasive. The Examiner is adjusting the restriction to linking claim analysis. However, Applicant is incorrect in the assertion that claim 1 links the claims and acts to prevent restriction between them. MPEP 809.03 states, the most common types of linking claims which, **if allowed,** act to prevent restriction between inventions that can otherwise be shown to

be divisible, are genus claims linking species claims. Thus a genus claim linking species claims does not preclude restriction. Claim 1 link(s) inventions SEQ ID NOs:1-6 (thrombin peptide derivatives). The Examiner has acknowledged the election of species SEQ ID NO:6. The Examiner will rejoin SEQ ID NO:5 and SEQ ID NO:6. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claim 1. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application.

Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The requirement is still deemed proper and is therefore made FINAL. Claims 6-10 and 20-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12. Claims 1-5, 11-19 and 41-46 are under examination.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR § 1.821 through 1.825 because:

a. the instant claims recite SEQ ID NO:5 and SEQ ID NO:6 as having a **Tyr** at position number three, however the raw sequence listing recites SEQ ID NO:5 and SEQ ID NO:6 as having a **Thr** at position number three.

b. the instant claims recite SEQ ID NO:5 as having 23 amino acids, however, the raw sequence listing recites 25 amino acids for SEQ ID NO:5.

c. the amended specification states (page 8, lines 1-3) that SEQ ID NO:6 has the identical amino acid sequence of SEQ ID NO:5 and also contains a C-terminal amide, however, the raw sequence listing recites different sequences for SEQ ID NO:5 and SEQ ID NO:6.

Applicant must provide a CRF and a paper copy of the Sequence Listing, as well as an amendment directing its entry into the specification. Applicant must also submit a statement that the content of the paper and computer readable copies are the same and include no new matter. Applicants is given the same response time regarding this failure to comply as that set forth to respond to this office action. **A complete response to this office action includes compliance with this sequence rule compliance.**

Applicant must submit a response to this Office Action and compliance with sequence rules simultaneously.

Based on the sequence problems associated with the instant application, it is unclear what Applicant intends by SEQ ID NO:5 and SEQ ID NO:6. For purposes of art, SEQ ID NO:5 and SEQ ID NO:6 were taken from the raw sequence listing of the computer readable form. The Examiner has enclosed a copy of the raw sequence listing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 11-19 and 41-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of stimulating bone growth at a site in a subject in need of osteoinduction, said method comprising the step of administering to the site a therapeutically effective amount of SEQ ID NO:5 or SEQ ID NO:6,

does not reasonably provide enablement for:

a method of stimulating bone growth at a site in a subject in need of osteoinduction, said method comprising the step of administering to the site a therapeutically effective amount of an agonist of the non-proteolytically activated thrombin receptor. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches PLGA microsphere containing TP508 (SEQ ID NO:5) induce bone formation in large defects in rabbit ulna (specification, pages 17-19). The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because the specification fails to teach that any agonist of non-proteolytically activated thrombin receptor, any thrombin peptide derivative or physiologically functional equivalent thereof can be used in the claim method (i.e. having the activity of stimulating bone growth).

Furthermore, the specification also fails to teach how to make any thrombin peptide derivative or physiologically functional equivalent thereof while still maintaining bone growth activity. The specification does not support claims to agonist of non-proteolytically activated thrombin receptor modified to an unlimited extent relative to those exemplified. It is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites (see Wells, 1990, Biochemistry 29:8509-8517).

The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, *etc.* in the disclosed sequence would afford a protein having activity comparable to the one disclosed. For sequences having one or two substitutions, for example, the artisan would reasonably expect that many of the possible variants would retain functional properties comparable to those of the unmodified protein, and it would require only routine manipulations to make and test a reasonably representative sampling of the possible variants. However, as the number of modified sites increases, the number of possible variants, and hence the degree of experimentation required, increases exponentially. Additionally, as plural substitutions are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically large number of possible structural variants had the functional properties of the claimed proteins. For the reasons discussed above, such experimentation would be undue for one skilled in this art.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the

unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1-5, 11-19, 41-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification provides adequate written description for SEQ ID NO:5 and SEQ ID NO:6, but not any thrombin peptide derivative or physiologically functional equivalent thereof.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of SEQ ID NO:5 and SEQ ID NO:6, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a

potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO:5 and SEQ ID NO:6, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 11, 12 and 35-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite. Claim 5 recites the method of claim 4 wherein the agonist consists of between about 12 and about 23 amino acids. The instant claim is indefinite in its recitation of closed (consist) and open language (between about 12 and about 23).

Claims 11 and 12 depend on claims drawn to a non-elected group. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 11, 12 , 14, 15 and 41-46 are indefinite. The claims are drawn to SEQ ID NO:5 and SEQ ID NO:6. The instant claims are indefinite because it is unclear what sequences are being claimed.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 11, 12, 19 and 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Simmons *et al.*, "Acceleration of Rat Femoral Fracture Healing by a Synthetic Thrombin Peptide", meeting held 20 November 1998 (IDS#AS3 submitted by Applicant, Paper No. 8). Simmons *et al.* teach a 23 amino acid fragment of human thrombin molecule (TP508; SEQ ID NO:5) which binds to the nonproteolytically-activated receptor for thrombin (page 4, 2nd paragraph)(claims 4, 5, 11, 12). Simmons *et al.* teach methods of administering TP508 to stimulate bone growth at a site in rats in need of bone repair due to fracture (page 5)(claims 1-3, 19, 41-43).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simmons *et al.* (IDS#AS3 submitted by Applicant) in view of Schmitz, US Patent No. 4,637,931. The teachings of Simmons *et al.* are described above. Simmons *et al.* do not teach implantable osteoconductive matrix comprising polylactic acid/polyglycolic acid homopolymer (PLA/PGA) or copolymer.

Schmitz teaches a method comprising implanting at the site of the broken osseous tissue a therapeutically effective amount of a composition comprising decalcified freeze dried bone incorporated into a biodegradable polymeric matrix of PLA/PGA (abstract and column 3, lines 6-29). Schmitz teaches that the copolymer-decalcified freeze dried bone implant material is successful at stimulating bone repair (column 6, lines 30-40). Schmitz teaches that the material may be osteoinductive (column 6, lines 55-66).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Simmons *et al.* and Schmitz to make the instant invention of a method for stimulating bone growth at a site comprising administering in a pharmaceutical composition an agonist of non proteolytically activated thrombin receptor and an implantable biocompatible carrier. The motivation and expected success is provided by both Simmons *et al.* and Schmitz. Simmons *et al.* teach a way to heal bone fractures using TP508 which avoids the risk of over stimulating target cells, which may happen upon administration of certain growth factors. Schmitz teaches the use of suitable carriers comprising matrices which induce migration of bone progenitor cells at sites of fractures.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-5, 11-19, 41-46 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5, 11-16, 35-43 of copending Application No. 09/909122. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD
August 5, 2003

YVONNE EYLER, PH.D
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